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PHARMACEUTICAL NANOTECHNOLOGY NOVEL NANOEMULSION –HIGH ENERGY EMULSIFICATION PREPARATION, EVALUATION AND APPLICATION

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ABSTRACT

The preparation, characteristics, evaluation and application of nanoemulsion are reviewed and summarized. Nanoemulsion consist of the fine oil in water or water in oil dispersion with surfactant and co-surfactant having droplets covering the size range of 20-600 nm and show narrow size distribution. High energy emulsification method achieved using high shear stirring, high pressure homogenizer, Jet dispersers, Microfluidizer, Ultrasound generators or Ultrasonication. Different oil in water (o/w) or water in oil (w/o) nanoemulsions was prepared by aqueous phase titration method. Prepared nanoemulsion were subjected to Thermodynamic stability tests for phase separation ,creaming ,cracking, coalescence or phase inversion and prepared nanoemulsion formulations were characterized in term of morphology ,droplets size, viscosity, pH, optical clarity, zeta potential ,conductivity, transmission electron microscopy, polydispersity. Pharmaceutical application in development of nanoemulsion formulation as Controlled drug delivery, Target drug delivery, Nutraceuticals, Food products, Transdermal, Liposome and Cosmetics.

Keywords: Nanoemulsion, High energy emulsification, Ultrasonication, Jet dispersers, Microfluidizer

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1.0 INTRODUCTION

Nanoemulsion or miniemulsion are fine oil/water or water/oil dispersion stabilized by an interfacial film of surfactant molecules having droplet covering the size range 20-600nm, due to their characteristic size nanoemulsion appear transparent or translucent to the naked eye. Nanoemulsion are not only kinetically stable but also long term physically stable which make them unique some times referred to as approaching thermodynamic stability. Nanoemulsion posses stability against creaming, flocculation, coalescence and sedimentation. Nanoemulsion formulated with oil, surfactant and cosurfactant are non toxic, non-irritant and approved for human consumption that are "generally recognized as safe" by the FDA.

One of the promising technologies is nanoemulsion drug delivery system, which is being applied to enhance

the oral bioavailability of the poorly soluble drugs. Nanoemulsion provides ultra low interfacial tensions and large o/w interfacial areas. Nanoemulsions have a higher solubilization capacity than simple micellar solutions and their thermodynamic stability offers advantages over unstable dispersions, such as emulsions and suspensions, and has a long shelf life. The nanosized droplets leading to enormous interfacial areas associated with nanoemulsions would influence the transport properties of the drug, an important factor in sustained and targeted drug delivery. The attraction of formulating o/w nanoemulsion systems lies in their ability to incorporate hydrophobic drugs into the oil phase thereby enhancing their solubility. Nanoemulsions have been reported to make the plasma concentration profiles and bioavailability of drugs more reproducible.

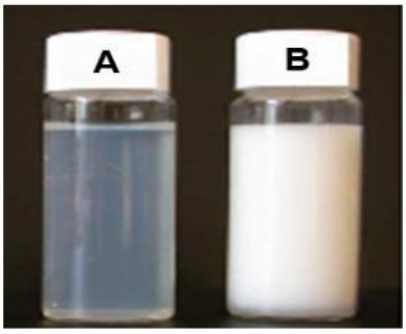
Due to small droplet size range nanoemulsion are able to penetrate easily through the skin layers and enhance skin penetration of incorporated drugs in TDDS.

Nanoemulsion is suitable for efficient delivery of active ingredients through the skin. The large surface area of the emulsion system, the low surface tension of the whole system and the low interfacial tension of o/w droplets allows enhancing penetration of active agent.

The fluidity nature of the system (at low oil concentration) as well as the absence of any thickeners may give them a pleasant aesthetic character and skin feel.

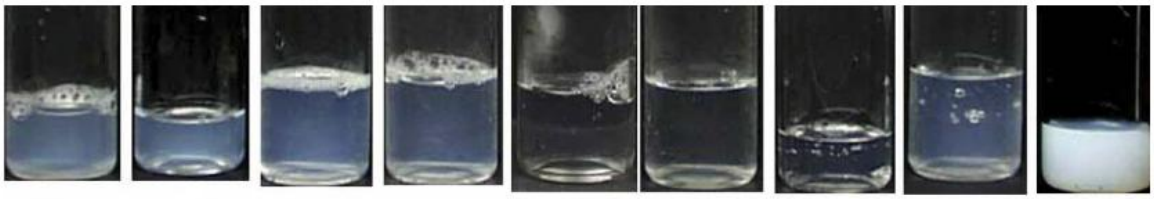
Nanoemulsion can be applied for delivery of fragrance, which may be incorporated in many personal care products. This could be applied in

perfumes, which are desirable to be formulated alcohol free.



(Fig. A nanoemulsion (a) and a macroemulsion (b) with droplet diameters of less than 100 nm and more than 1000 nm, respectively

Nanoemulsion may be applied as a substitute for liposome's and vesicles (which are much less stable) and it is possible in some cases to build lamellar liquid crystalline phase around the nanoemulsion droplets.



Nanoemulsion constitutes primary step in nanocapsules and nanospheres synthesis using nanoprecipitation and the interfacial polycondensation combined with emulsification.

The following are examples of most recent proposals of drug solubilized in nanoemulsion for disease treatment; anticonvulsant, antihypertensive, antibiotics, anti-inflammatory applied through skin.

2.0 MATERIALS AND METHODS

Generally oils, surfactant and cosurfactants are used as a excipients in the preparation of nanoemulsion which impart a specific role in the formulations.

The oil represents important excipient in nanoemulsion formulation because it can solubilize lipophilic drugs transport via the intestinal lymphatic system. Triglycerides vegetable oils ingested in food fully digested and absorbed and therefore do not present safety issue.

Nonionic surfactants are generally used nanoemulsion formulation because they are less toxic than ionic surfactant. They are usually accepted for oral ingestion and better drug solvency

In most case single chain surfactant alone are not able to reduce the oil/water interfacial tension sufficiently to form nanoemulsion the co-surfactant is an amphiphile with an affinity for both the and aqueous phase and partition to an appreciable extent into the surfactant interfacial monolayer present at the oil/water interface. They have further reducing the interfacial tension increasing the fluidity of the interface thereby increasing the entropy of the system. The commonly used oils, surfactants and co-surfactants are listed below

2.1 Pharmaceutically acceptable excipients

	Brand name	Chemical name	HLB value
Oils	Sesame oil		
	Castor oil		
	Soya bean oil		
	Corn oil		
	Olive oil		
	Isopropyl myristate	Tetradecanoic acid	
	Capryol 90	Propylene Glycol Monocaprylate	6
	Labrafac Lipophile WL1349	Medium Chain Triglycerides	2
	Methyl decanoate		
	Methyl oleate		
	Ethyl oleate		
	Maisine 35-1	Glyceryl Monolinoleate	4
	Peceol	Glyceryl Oleate	3
	Captex 200	Propylene glycol dicaprylate/ dicaprate	
	Miglyol 812	Caprylic/Capric Triglyceride	
	Sefsol 218		
	Triacetin	Glycerol triacetace	
	Carbitol		
	Capmul MCM	Glycerol monocaprylate	5-6

Surfactant	Cremophor EL	Polyoxyl 35 castor oil	12-14
	Solutol HS-15		
	Tween 20	Polyoxyethylene sorbitan fatty acid esters	
	Tween 80	Polyoxyethylene (20) sorbitan mono oleic acid	15
	Labrasol	PEG-8 caprylic/capric glycerides	14
	Poloxamer 407		
	Polaxmer 188		
	Span 20	sorbitan fatty acid esters	
	Span 80		
	Emulphor-620		
	Gelucire® 44/14	Lauroyl Macrocegolglyrides (Polyoxylglycerides)	14
	Cremophor RH40®	Polyoxy ethylene 40 hydrogenated castor oil	14-16
Co-surfactant	Propylene glycol		
	Polyethylene glycol		
	Labrafil M1944CS	Oleoyl Macrogolglycerides (Polyoxylglycerides)	4
	Plurol oleique CC497	Polyglyceryl Oleate	6
	Lauroglycol 90	Propylene Glycol Monolaurate	5
	Imwitor 742		
	Akoline MCM		
	Akomed E		
	Transcutol P	Diethylene Glycol Monoethyl ether	
	Capmul MCM-C8	Medium chain mono- and diglycerides of caprylic acid	
	Lauroglycol™ FCC	Propylene Glycol Laurate	4
	DUB GPE AB	Apricot kernel oil PEG-6 esters	

2.2 METHODS

Nanoemulsion, being non-equilibrium systems cannot be formed spontaneously. Consequently, energy input generally from mechanical devices or from the chemical potential of the components is required, Nanoemulsion formation by the so

called dispersion or high energy emulsification method is generally achieved using high shear stirring, high pressure homogenizers and ultrasound generators.

It has been shown that the apparatus supplying the available energy in the shortest time and having the most homogeneous flow produces the smaller sizes. High pressure homogenizers meet these requirements; Therefore, They are the most widely used emulsifying machines to prepare nanoemulsion.

Generally, the conventional high pressure homogenizers work in a range of pressures between 50 and 100 Mpa. Pressures as high as 350Mpa have been achieved in a recently developed instrument.

Ultrasonication emulsification is also very efficient in reducing droplet size but it is appropriate for small batches. On the preparation of polymerizable nanoemulsion has shown that the efficiency of dispersion process is strongly dependent on ultrasonication time at different amplitudes and that the more hydrophobic the monomer is the longer the sonication time required.

2.2.1 ULTRASONIC SYSTEM

In ultrasonic emulsification, the energy input is provided through so called sonotrodes (sonicator probe) containing piezoelectric quartz crystals that can be expand & contract in response to alternating electrical voltage. As the tip of sonicator probe contacts the liquid, it generates mechanical vibration and therefore cavitations occurs, which is the main phenomenon responsible for ultrasonically induced effects.Cavitation is the formation and collapse of vapour cavities in a flowing liquid.. Such a vapour cavity forms when the local pressure is reduced to that of at the temperature of the flowing liquid because of local velocity changes. The collapse of these cavities causes powerful shock waves to radiate throughout the solution in proximity to the radiating face of the tip, thereby breaking the dispersed droplets.

Within the ultrasound range, the power available varies inversely with the frequency and only powerful ultrasound (0-200kHz) is able to produce physical and chemical changes such as emulsification.

Ultrasound can be used directly to produce emulsion, but since breaking an interface requires a large amount of energy, it is better to prepare coarse emulsion before applying acoustic power. Due to small product throughput the ultrasound emulsification process mainly applied in laboratories where emulsion droplet size as low as 0.2 micrometer can be obtained.

2.2.2 MICROFLUIDIZER

It is possible to produce emulsion at much higher pressures up to approximately 700 Mpa, in the nozzle of microfludizer that is the heart of this device (the interaction chamber), two jets of crude emulsion from two opposite channels collide with one another. The process stream is delivered by a pneumatically powered pump that is capable of pressurizing the in-house compressed air (150-650 Mpa) up to about 150 Mpa. Forcing the flow stream by high pressure through microchannels toward an impingement area creates a tremendous shearing action, which can provide an exceptionally fine emulsion

2.2.3 JET DISPERSER

Forcing the flow stream by high pressure through microchannels towards an impregnated area creates a tremendous shearing action, which can provide an exceptionally fine emulsion. In general, initial forces in turbulent flow along with cavitations are predominantly responsible for droplet disruption in microfluidizer. Disruption in laminar elongational flow is also possible, especially when emulsion has high viscosity.

In the jet disperser two or more jets of crude emulsion each from opposing bores collide with one another but at a different design than microfludizer, the diameter of the bores injet dispersers are typically 0.3-0.5mm. Finally an "orifice plate" is the simplest construction form for a homogenizing nozzle. The diameter of orifice bore is of same order of magnitude as the jet dispersers and inlet head diameter of orifice plate is typically 10-60nm, In jet dispersers & orifice plates, droplets are disrupted predominantly due to laminar elongational flow ahead of the bores. Unlike radial diffusers, the nozzle is microfluidizers; jet dispersers and orifice plate contain no moving parts, so they can be used at high pressures up to 300-400 Mpa.

2.3 COMPARISION OF THE EMULSIFICATION SYSTEMS

The emulsifying devices have a wide variety of design & functional capability, the choice being determined by number of factors, including emulsion volume, viscosity of emulsion & its phases, surfactant type & concentration, temperature consideration, final emulsion droplet size & size distribution. After choosing the most suitable emulsifying device, the operating condition such as flow rate, pressure, gap-thickness, temperature emulsification time & rotation speed should be optimized to obtain desired emulsion.

2.4 COMPARISON OF DIFFERENT TYPES OF EMULSIFICATION SYSTEMS

Emulsification system	Rotor–stator systems	High-pressure systems	Ultrasonic systems	Membrane systems
Examples	Mixers, agitators, colloid mills (Silverson, Ultra-Turrax)	Radial diffusers, valve homogenizers, jet dispersers, microfluidizer	Sonotrodes (sonication probes)	Glass/ceramic membranes
Droplet disruption mechanisms	Shear stress in laminar flow and/or shear and inertial stress in turbulent flow	Shear and inertial stress in turbulent flow; cavitation in laminar extension flow	Cavitation in microturbulent flows	Dispersed-phase flux
Throughput	Medium to high	High	Low	Low
Batch/continuous	Batch (mixers) or continuous (colloid mills)	Continuous	Batch or quasi-continuous	Continuous
Minimum droplet size (μm)	1.0	0.1	0.1–0.2	0.2–0.5
Optimal range of viscosity	Low to high (20–5000mPas)	Low to medium(1–200 mPa s)	Low to medium	Low to medium
Application	Lab/industrial	Lab/industrial	Lab	Lab
Dominant flow regime	LV,	TV TI, TV (CI, LV)	CI	Injection
Energy density	Low–high	Medium–high	Medium–high	Low–medium
Change of energy input	Rotation speed, exposure	Pressure, recirculation	Intensity and frequency of	Pore diameter
Through	time, gap distance, and disk	(exposure time), and nozzle	ultrasonic wave sonication	
	design	design	time	
Residence time in dispersing zone, t	0.1<t<1 s	0.1<t<3ms	–	–
Required adsorption rate	Low to high	High to very high	Middle to high	Middle to high
of emulsifier				

2.5 SOLUBILITY STUDY

The solubility of drugs in various oils, surfactants, co-surfactant (given in table) was determined by dissolving an excess of drug in 2ml of each of selected oils, surfactants, co-surfactant in 5ml stoppered vials. Combinations of oils were also used for solubility determination. Excess amount of drug was added to each 5ml stoppered vials and mixed using vortex mixer. The vials were then kept at 37±1°C in a isothermal shakers (Nirmal International, India) for 72 hours to get to equilibrium. The equilibrated samples were removed from the shaker and centrifuged at 3000 rpm for 15 min. The supernatant was taken and filtered through a 0.45 micrometer membrane filter. The concentration of drug was determined in each solution by HPLC or UV spectrophotometer at particular λmax.

SOLUBILITY TABLE OF ACECLOFENAC

Excipients	**Solubility Mean ± SD (mg/mL)**
Triacetin	8.22 ± 1.12
Labrafil + Triacetin (2:1)	48.95 ± 2.22
Labrafac	6.31 ± 0.52
Labrafil + Triacetin (3:1)	39.44 ± 1.98
Oleic acid	4.01 ± 0.92
Labrasol	386.45 ± 3.28
Labrafil	32.56 ± 2.43
Tween80	398.21 ± 2.89
Iso-propyl myristate	2.97 ± 1.01
Cremophor EL	272.32 ± 2.94
Olive oil	1.69 ± 0.35
Transcutol P	292.42 ± 2.80
Labrafil + Triacetin (1:1)	35.24 ± 2.14

Dispersibility test

The efficiency self emulsification of oral nanoemulsion was assessed

Emulsification system	Rotor–stator systems	High-pressure systems	Ultrasonic systems	Membrane systems
Examples	Mixers, agitators, colloid mills (Silverson, Ultra-Turrax)	Radial diffusers, valve homogenizers, jet dispersers, microfluidizer	Sonotrodes (sonication probes)	Glass/ceramic membranes
Droplet disruption mechanisms	Shear stress in laminar flow and/or shear and inertial stress in turbulent flow	Shear and inertial stress in turbulent flow; cavitation in laminar extension flow	Cavitation in microturbulent flows	Dispersed-phase flux
Throughput Batch/continuous	Medium to high Batch (mixers) or continuous (colloid mills)	High Continuous	Low Batch or quasi-continuous	Low Continuous
Minimum droplet size (μm)	1.0	0.1	0.1–0.2	0.2–0.5
Optimal range of viscosity	Low to high (20–5000mPas)	Low to medium(1–200 mPa s)	Low to medium	Low to medium
Application Dominant flow regime	Lab/industrial LV,	Lab/industrial TV TI, TV (CI, LV)	Lab CI	Lab Injection
Energy density Change of energy input Through	Low–high Rotation speed, exposure time, gap distance, and disk design	Medium–high Pressure, recirculation (exposure time), and nozzle design	Medium–high Intensity and frequency of ultrasonic wave sonication time	Low–medium Pore diameter
Residence time in dispersing zone, t	0.1<t<1 s	0.1<t<3ms	–	–
Required adsorption rate of emulsifier	Low to high	High to very high	Middle to high	Middle to high

2.6 SOLUBILITY STUDY

The solubility of drugs in various oils, surfactants, co-surfactant (given in table) was determined by dissolving using a STD USP XXII dissolution apparatus 2. One ml of each formulation Was added to 500 ml of water at 37°C+-0.5°C. A standard stainless steel dissolution paddle rotating at 50 rpm provided gentle agitation. The in vitro performance of the formulation was visually assessed using the following system.

GRADE A:-Rapidly forming, nanoemulsion having clear or bluish appearance.

GRADE B:-Rapidly forming, slightly less clear emulsion having a bluish white appearance.

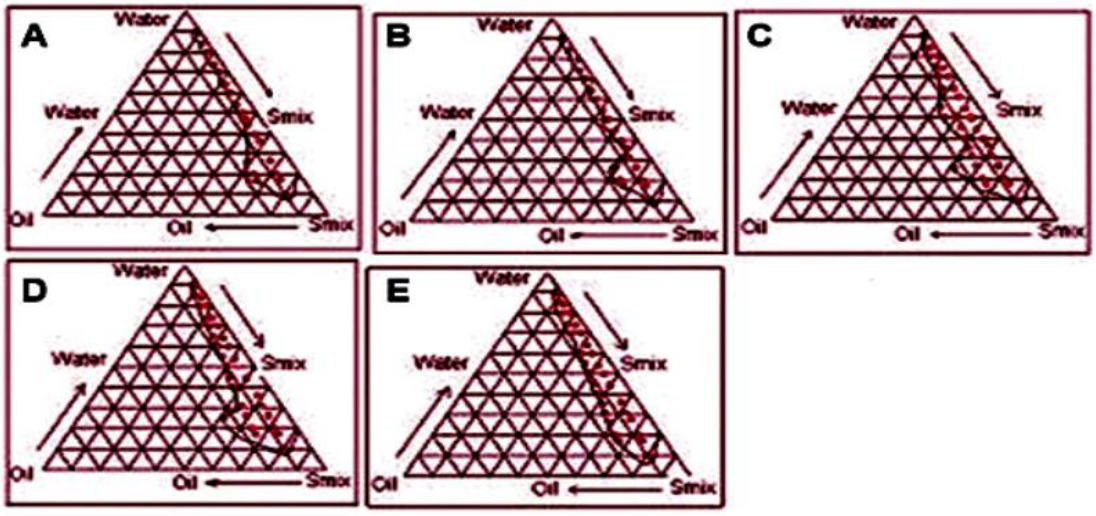
GRADE C:-Fine milky emulsion.

GRADE D:-Dull, grayish white emulsion having slightly oily appearance that is slow to emulsify

GRADE E:-Formulation, exhibiting either poor or minimal emulsification with large oil globules present on the surface.

2.7 PSEUDO-TERNARY PHASE DIAGRAM

On the basis of solubility studies single or a compilation of oils was selected as the oil phase, as well as surfactants and cosurfactant, respectively. Distilled water was used as an aqueous phase, surfactants and cosurfactant (Smix) was mixed at different ratios (1:1, 1:2, 1:3, 1:4, 2:1, 3:1, 4:1). These ratios were chosen in increasing concentration of surfactant with respect to cosurfactant and vice-versa for detailed study of phase diagram. For each phase diagram oil and Smix at a specific ratio was mixed thoroughly at different mass ratios from 1:9 to 9:1 in different glass vials.



2.8 PERCENTAGE TRANSMITTANCE

The percentage transmittance of the optimized formulation was determined. The formulation had the highest percentage transmittance or close to 100% indicated that formulation was clear and transparent. Percentage

Transmittance of the prepared nanoemulsion formulation was determined spectrophotometrically. One ml of the formulation was diluted 100 times using solvent and analyzed at λmax using solvent as blank.

2.9 THERMODYNAMIC STABILITY STUDIES

(1). Heating cooling cycle :- Six cycle between refrigerator temperature 4°C & 45°C with storage at each temperature of not less than 48 h was studied. Those formulation which are stable at these temperature, were subjected to centrifugation test.

(2). Centrifugation: - Passed formulation was centrifuged at 3500 rpm for 30 min. Those formulations did not show any phase separation was taken for freeze thaw stress test.

(3). Freeze thaw cycle :- Three freeze thaw cycle between -21°C & 25°C with storage at each temperature for not less than 48 h was done for the formulation. Those formulation which passed thermodynamic stress test, were further taken for dispersibility test for assessing the efficiency of emulsification.

2.10 DROPLET SIZE & SIZE DISTRIBUTION

Droplet size & size distribution depends on the rate of emulsification process but also for the volume and the particle size distribution of produced emulsion. The emulsification process depends mainly on following variables:-

- Interfacial tension
- Interfacial and bulk viscosity
- Phase transition region
- Surfactant structure and concentration

Emulsification is produced by different mechanism which seems to be affected by system composition & their physico-chemical characteristics. The formulation (0.1ml) was dispersed in 50ml of water in volumetric flask. Globule size of the nanoemulsion was determined by correlation spectroscopy that analyzes the fluctuation in light scattering due to Brownian motion of the particles. Using a zetasizer 100 HS (Malvern instrument,UK). Light scattering was monitored at 25°C at a 90° angle.

The globule size increased with increase in concentration of oil in the formulation. Droplet size was calculated from the volume size distribution.

Droplet size analysis Droplet size is thought to have an effect on drug absorption, the smaller size, larger the interfacial surface area will be provided for drug absorption, several variables on droplet size including dilution volume, different media, drug concentration (drug loading) and dispersing method.

The effect of dilution on droplet size in distilled water was measured. When dilution time 1000 fold, the droplet size seemed to be unchanged, which revealed that the nanoemulsion formed on dilution was as large as 1000 times capable of keeping drug solubilized.

As drug loading increased from 0.2 to 2.5% the droplet size remained almost unchanged, which indicate that the drug loading had no obvious effect on droplet size in water. The effect of medium on droplet size was also investigated. When the nanoemulsion dispersed in distilled water, 0.9% NaCl, 0.1N HCl and 6.8 phosphate buffers, the resulted droplet size was 24.1±3.6nm, 25.6±1.7nm, 25.9±1.8nm, 25.7±3.3nm respectively. There is no significant difference among the four different media, which demonstrated that the formulation was not affected by pH and ionic strength. The effect of various mixturing ways including oscillate whisk (25rpm, 50rpm, 100rpm) and swirt seems to have no effect.

2.11 ZETA POTENTIAL

Emulsifiers not only act as a mechanical barrier but also through formation of surface charges zeta potential, which can produce repulsive electrical forces among approaching oil droplets and this hinders coalescence. The more negative zeta potential, greater the net charge of droplets and more stable the emulsion is. Zeta potential values lower than -30 mv generally indicate a high degree of physical stability.

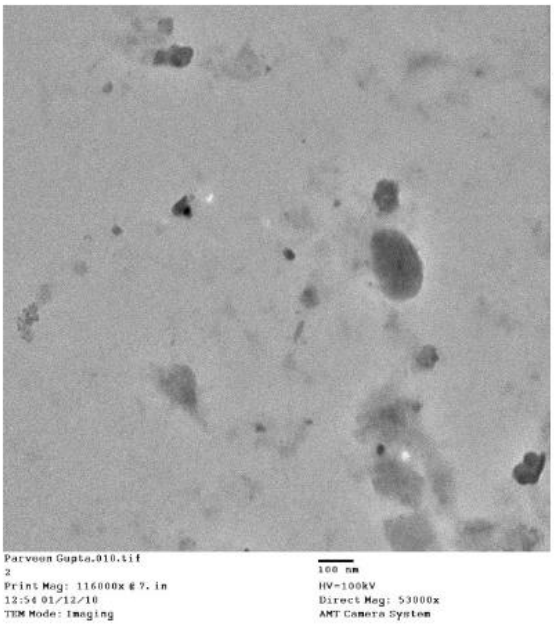
It should be noted that a comparison of the zeta potential with the particle size results showed in general, that a decrease in a particle sizes of emulsion was accompanied by a decrease in negative surface charge values.

The droplets size and zeta potential are the more representative parameters in the control of emulsion stability. To evaluate the emulsion stability, these aspects were monitored over 3 months.

2.12 TRANSMISSION ELECTRON MICROSCOPY (TEM)

Morphology and structure of the nanoemulsion were studied using transmission electron microscopy (TEM) TOPCON 002B operating at 200 KV capable of point to point reduction. Combination of bright field imaging at increasing

magnification and of diffraction modes was used to reveal the form and size of the nanoemulsion. In order to perform the TEM observation the nanoemulsion formulation was diluted with water (1/100). A drop of diluted nanoemulsion was then directly deposited on the holely film grid and observed after drying. The emulsion appears dark and the surroundings are bright a "positive" image is seen. The direct observation also enabled us to perform selected area electron diffraction (SAED) to check the crystallinity of the emulsion core components. TEM fig of Diclofenac diethylammonium given below.



2.13 POLYDISPERSITY

Polydispersity is the ratio of standard deviation to mean droplet size, so it indicates the uniformity of droplet size within the formulation. The higher the polydispersity, the lower the uniformity of the droplet size in the formulation.

$$\text{Span} = \frac{D(0.9) - D(0.1)}{D(0.5)}$$

Where D(0.9) corresponds to particle size immediately above the sizes of 90% of nanodroplets D(0.5) sizes of 50% of the nanodroplets and D(0.1) corresponds to particle size immediately above sizes of 10% of nanodroplets

2.14 REFRACTIVE INDEX

Refractive index of placebo formulations (without drugs), drug loaded formulation and one year old formulation was using abbes type refractometer (Nirmal International).

When the refractive index values for formulation were compared with those of placebo and one year old formulation, it was found that there were no significant differences between the values, therefore it can be concluded that the nanoemulsion formulation were not thermodynamically stable but also chemically stable and remain isotropic; thus there were no interaction between nanoemulsion excipients and drug.

2.15 VISCOSITY DETERMINATION

The viscosity of nanoemulsion formulation generally was very low .This was expected, because one of characteristics of nanoemulsion formulation is lower viscosity.

The viscosity of formulation (0.5 g) was determined without dilution using Brookfield DV III Ultra V6.0RV cone and plate rheometer (Brookfield engineering laboratories) Inc; Middle boro MA), using spindle # CPE 40 at 25+_0.5 °C. The software used for this calculation was Rheocalc V2.6.

2.16 DRUG CONTENT

Preweighed Nanoemulsion was extracted by dissolving in 25ml suitable solvent, extract was analyzed by spectrophotometrically/ H.P.LC. against the standard solution of drug.

2.17 CONDUCTIVITY MEASUREMENT

A conductometer (cloud 315i WTW Germany) was used in non-linear temperature compensation mode, according to EN 27888 conductivity was determined during heat between 45 & 90°C under magnetic stirring at an agitation of 250 rpm. This temperature ranges permit a steady state to be achieved, either as an emulsion o/w (high steady state) or as an emulsion w/o (low steady state) in different condition tested. The recording of conductivity relative to temperature permits the determination of phase inversion temperature. Conductivity values lower than 10 micro cm^{-1} means that the continuous phase is oil, where as a highly steady state shows that water is the continuous phase.

2.18 APPLICATION

Nanoemulsion are of great interest as Pharmaceutical, Drugs, Nutraceuticals, Food products & cosmetics formulation. Nanoemulsions are used as drug delivery system for administration through various routes. Parentral, Oral, Topical, Ocular, Pulmonary, Mucosal, Cosmetic, Transdermal, Controlled &Target

2.19 PARENTRAL

Nanoemulsion are advantages for intravenous administration, due to the strict requirement of this route of administration, particularly the necessity for the formulation droplet size lower than 1 micrometer

Parenteral (or Injectable) administration of nanoemulsion is employed for a variety of purposes, namely nutrition eg. Fats, Carbohydrates, Vitamins etc.Nanoemulsions of natural oils(soyabean, sesame and olive) with the non toxic surfactant Pluronic F-68 via ultrasound for parentral feeding.Lipid nanoemulsion has been widely explored for parentral delivery of drugs.

2.20 ORAL

The benefit of Nanoemulsion in the oral administration of drugs has been also reported and the absorption of the emulsion in the gastrointestinal tract has been correlated to their droplet size and surface area.Primaquine when incorporated into oral lipid nanoemulsion showed effective antimalarial activity against Plasmodium bergheii infection in mice at a 25% lower dose level as compared to conventional oral dose.Lipid nanoemulsion of primaquine improved oral bioavailability by the liver with drug concentration higher at least by 45% as compared with the plain drug.

Nanoemulsion is also used as ocular delivery system to sustain the pharmacological effect of drugs in comparison to their respective solution.

Cationic nanoemulsion was evaluated as DNA vaccine carriers to administer by pulmonary route.

They are also interesting candidate for the delivery of drugs or DNA plasmids through the skin after topical administration (TDDS).

2.21 COSMETIC

The aesthetic properties, i.e. low viscosity and transparent visual aspects of nanoemulsion with droplet sizes below 200nm, its high surface area allowing effective transport of the active ingredient to the skin make them especially attractive for their application in cosmetics. Nanoemulsions are acceptable in cosmetics because there is no inherent creaming, sedimentation, flocculation or coalescence that are observed with macro emulsion. The incorporation of potentially irritating surfactants can be avoided by using high energy equipment during manufacturing. Nanogel technology to create miniemulsion from oil-in water concentrate suited to minimizing transepidermal water loss , enhanced skin protection and penetration of active ingredient. It would be useful for sun care products, moisturing and antiageing creams. It helps to give skin care formulations a good skin feels.

2.22 TRANSDERMAL

Indomethacin a potent NSAID, the anti-inflammatory effects of true optimized nanoemulsion formulation were compared with marketed gel in carragenan induced paw edema in rats.The %inhibition value was significant for developed Nanoemulsion, so great potential for transdermal application of indomethacin.Nanoemulsions for transdermal delivery of celecoxib.Formulation which consisted of 2% celecoxib 10% oil phase(Sefsol 218 and Triacetin) 50% surfactant mixture (Tween80 and Transcutol –P) and 40%water.The anti-inflammatory effect and percent inhibition value after 24h administration was found to be high for nanoemulsion formulation(81.2%) as

compared to celecoxib gel (43.7%) and nanoemulsion gel(64.5%). The in vitro-in vivo studies revealed a significant increase in the anti-inflammatory effects of aceclofenac nanoemulsion(82.2%) as compared to nanoemulsion gel formulation(71.4%)and conventional gel(41.8%).

2.23 TOPICAL

The nanoemulsion can achieve a level of topical antimicrobial activity that has only been previously achieved by systemic antibiotics. The antimicrobial nanoemulsions are oil and water and are stabilized by surfactants and alcohol having droplet size range 200-600nm.The nanoemulsion has broad spectrum activity against bacteria(e.g. E.coli, S.aureus) fungi (e.g. Candida, Dermatophytes).

The preparation & liquid core capsules which have application in efficient encapsulation and controlled delivery of a wide range of drugs, dyes etc. has also been achieved in nanoemulsion. Scottet.et.al (52) have reported an interfacial free direct encapsulation of liquid oil droplets of nanoemulsion within nanometer- thick polymer shell to localize the polymerization at oil-water interface of nanoemulsion , the polymerization at the oil-water interface of the nanoemulsion, the polymerization was initiated by an interface active azo-initiator.

3.0 LIST OF VARIOUS APPLICATIONS

Compound	Formulation	Related study design	Observation	Reference
γ-tocophenol	Phosphatidylcholine, soybean oil, sodium pyruvate polysorbate80,water	γ-tocopherol reduced auricular thickness (60%) with NE	Bioavailability for γ - tocopherol enhenced 2.2 with NE compared suspension	Nicolosi R. Jetal int. J.pham. 2008,363,206-213
saquinavir	Polyunsaturated fatty acid-oil lipoid-80 and deoxycholic acid &water	In mice 200µgSQV oral and 1µc of radioactive material by oralgavage	NE were 3 fold higher BA As compared to the control aq. suspension	Amiji.M et.al Int.J.Pharm 2008,347:93-101
Q10 Coenzyme	Cetylpalmitate,labrasol, miglyol, methanol ,tegoTHF ,water			
Prednicarbate	Phytospningosine tween80, lecithin,eutanol water, α - tocopherol ,lipoidE80		Optimal production parameter production temp. 50C 300 bar homogenization pressure 10 homogenization cycle	
Hydrogenated lecithin	Silicone oil, tween80,liquid paraffin	High shear homogenizer&	High dermal safety	

		microfluidizer general emulsion		
Lecithin based NE fludro cortisone acetate, flumethasone pivalate	Sucrose laureate &polysorbate80,cationic phytosphingosine,lipoidS75 containing 69.9% phosphatidylcholine	An enhancement factor 1.1&1.5 was obtained in relation to the control by high pressure homogenization		
δ- tocopherol	Canola oil, tween80, water,	Microfluidizer, Syrian golden hamsters	NE increase 36 times more plasma level than microemulsion(9fold),increase bioavailability transdermally applied δ- tocopherol	Nicolosi R. Jetal int. J.pham. 2008,347 ;144-148
Camphor menthol& Methyl salicylate	Soyabean oil tween 80 ,poloxamer 407 & propylene glycol and water	high pressure homogenization	The permeation rate of camphor from Hydrogel-thickened nanoemulsion system had the highest rate of 147.8±7.3µg/ cm^2h which showed statistically significant of control gel	Huabing Chen* ,International Journal of Pharmaceutics 353 (2008) 270–276
Primaquine diphosphate	Miglylol,Ovathin 160, Topcthin, Poloxamer 188, sorbitol and solvents of AR grade.	Antimalarial activity of oral lipid nanoemulsion containing primaquine having particle size in the range of 10–200 nm against Plasmodium bergheii infection in swiss albino mice at a 25% lower dose level as compared to conventional oral dose	Lipid nanoemulsion of primaquine exhibited improved oral bioavailability and was taken up preferentially by the liver with drug concentration higher at least by 45% as compared with the plain drug.	Kamalinder K. Singh et.al, International Journal of Pharmaceutics, (200)
Curcumin	Medium chain triacylglycerol, Tween 20, Milli-Q water.	The enhanced anti-inflammation activity of curcumin encapsulated in O/W emulsions is	There is a 43% or 85% inhibition effect of 12-O-tetradecanoylphorbol-13-acetate (TPA)-induced edema of mouse ear for 618.6 nm and	Xiaoyong Wang et.al, Food Chemistry, (2008)

		evidenced by the mouse ear inflammation model.	79.5 nm 1% curcumin O/W emulsions, respectively, but a negligible effect is found for 1% curcumin in 10% Tween 20 water solution.	
Risperidone (RSP)	Capmul. Tween 80, Polyethylene glycol 400 Polycarbophil, Transcutol, Diethylene triamine penta acetic acid (DTPA),Stannous chloride dihydrate, Sodium pertechnetate, separated from molybdenum-99	Biodistribution of RNE, RMNE, and risperidone solution (RS) in the brain and blood of Swiss albino rats following intranasal (i.n.) and intravenous (i.v.) administration was examined using optimized technetium labeled (99mTc-labeled) RSP formulations.	Studies conclusively demonstrated rapid and larger extent of transport of RSP by RMNE (i.n.) when compared to RS (i.n.), RNE (i.n.) and RNE (i.v.) into the rat brain.	Mukesh Kumar et.al International Journal of Pharmaceutics, (2008)
Aspirin	Soybean oil, Polysorbate 80.	Nano-emulsion preparations of aspirin prepared with a Microfluidize Processor were	Results showed that particle size (90 nm) populations of nanoemulsion preparations of aspirin compared to an aspirin suspension (363 nm), significantly decreased (pb0.	Balajikarthick Subramanian et.al, International Immunopharmacology, (2008)

		evaluated in the croton-oil-induced ear edema CD-1 mouse model using ear lobe thickness	05) ear lobe thickness approximately 2 fold greater than the aspirin suspension.	
Beta-Carotene	Medium chain triglyceride (MCT) oil, Tween 20, Tween 40, Tween 60, Tween 80.	Characterization and stability evaluation of Beta-carotene nanoemulsions prepared by high pressure homogenization under various emulsifying conditions	The particle sizes decreased with increases in homo-genization pressure and cycle, and also with temperature up to 50 _C. The physical stability of the nanoemulsions decreased with the elevation of temperature but increased with pressure (up to 100 MPa) and homogenization cycle (up to three cycles)	Yuan Yuan et.al, Food Research International, (2008)

REFRENCES

1) Kumar M, Mishra A, Pathak K et.al Intranasal nanoemulsion based brain targeting drug delivery system of resperidone Int J Pharm. 2008; 358:285-291.
2) Ruktanonchai U, Sakulku U, Nuchuchua o, et.al characterization and mosquito repellent activity of citronella oil nanoemulsion Int. J Pharm.2009.
3) Tajima K, Imai Y, Ujiie N et.al. Three phase structure of hexadecane nanoemulsion formed with Phospholipid-surfactant mixtures and its novel Phase transition temperature TE colloids and surfaces 2006; 276:134-142.

4) Maranhao R.C, Mendes.S, Graziani S.R, et.al. Uptake by breast carcinoma of a lipidic nanoemulsion after intralesional injections into the patients: Anew strategy for neoadjourant chemotherapy Gynecologic On cology 2009; 112:400-404.
5) Borchert H.H, Yilmaz E, et.al Design of a phytosphingosine containing positively charged nanoemulsion as a colloidal carrier system for dermal application of ceromides Eur. J Pharm, Bipharm. 2005; 60:91-98.
9) and charactrization of o/w nanoemulsion with natural oils and pluronic f68 as surfactant food hydrocolloids 2009; 23:1096-1102.
10) Nicolosi R, Kotyla T, Wilson T,et.al, Enhancement of anti-inflammatory property of aspirin in mice by a nanoemulsion preparation Int Immuno Pharmacol. 2008; 8:1533-1539.
11) Tang X Li F, Wang T,et.al The properties of bufadienolides-loaded nanoemulsion and submicron emulsion during lyophilization. Int J Pharm. 2008; 349: 291-299.
12) Mao L, Yacan Y, Gao Y, et.al, Characterisation and stability evaluation of B-Carotene nanoemulsions prepared by high pressure homogenization under various emulsifying conditions food.Res.Int.2008; 41:61-68.
13) Jafari SM, Assadpoor E, Bhandari B, et.al, Recoalescene of emulsion droplets during
6) Huang Q, Wang X, Jiang Y, et.al . Enhancing anti-inflammation activity of curcumin through o/w nanoemulsion Food Chemistry 2008; 108:419-424
7) Nicolosi R, Kotyla T, Kuo F et.al Increased Bio-availability of a transdermal application of a nano sized emulsion preparation Int. J Pharm 2008; 347:144-148.
8) Rodriguez M, Wulff-perez M, Gomez T et.al stability of emulsion for parental feeding : Preparation
high energy emulsification food hydrocolloids 2008; 22: 1191-1202.
14) Chen H, Mou D, Du D, et.al Hydrogel thickened nanoemulsion system for topical delivery of lipophilic drugs Int. J. Pharm. 2008; 353:270-276.
15) Valenta C, Holler S, Sperger A Lecithin based nanoemulsions: A comparative study of the of non-ionic surfactants and the cationic phytosphingosine on physicochemical behaviour and skin permeation Int. J. Pharm. 2009; 370:181-186.
16) Park S.J, Bae D.H, Shin J.S, et.al. Effect of Lecitin on Dermal safety of Nanoemulsion prepared from Hydrogenated Lecithin and Silicone Oil Bull. Korean Chem. Soc. 2009: 30:821-824.
17) Anton N, Saulnier P, Benoit J.P. Design and production of nanoparticles formulated from

nanoemulsion templates. A review J.Cont. Rel.2008; 128:185-199.

18) Basphinar Y, Keck M.C, Borchert H.H, Development of a positively charged prednicarbate nanoemulsion Int. J. Pharm. 2010; 383:201-208.

19) Junyaprasert B.V, Muller H.R, Souto B.E et.al.Q10 loaded NLC versus nanoemulsions; stability, rheology and in vitro skin permeation. Int. J Pharm. 2009; 377:207-214.

20) Constantinides P.P, Chaubal V.M, Shorr R, Advances in Lipid nanodispersions for parental drug delivery and targeting. Adv. Drug Del. Rev. 2008; 60:757-767.

21) Vyas T.K, Amiji M.M, Shahiwala A, Improved oral bioavailability and brain transport of saquinavir upon administration in novel nanoemulsion formulations Int. J. Pharm 2008; 347:93-101.

22) Leong T.S.H, Kentish S.E, Wooster T.J, et.al. Minimizing oil droplet size using ultrasonic emulsification Ultra Sonochem. 2009; 16:721-727.

23) Aubrun O.S, Simonnet J.T, Alloret F.L, Nanoemulsions: a new for skincare products Ad. Collo. Inter Sci 2004; 108-109:145-149.

24) Nicolosi J.R, Kuo F, Kotyla T, et.al. Nanoemulsion of an anti-oxidant synergy formulation containing gamma tocopherol have enhanced bioavailability and anti-inflammatory properties Int J. Pharm. 2008;363:206-213.

25) Rapoport Y.N, Kennedy M.A, Scaife L.C, et.al. Controlled and targeted tumor chemotherapy by ultrasound activated nanoemulsions/microbubbles J.Cont.Rel. 2009; 138:268-276.

26) Nabi S.S, Shakeel F, Talegaonkar S,et.al . Formulation Development and optimization using Nanoemulsion Technique: A technical Note AAPS Pharm Sci Tech 2007; 28:E1-E6.

27) Shakeel F, Baboota S, Ahuja A, et.al. Nanoemulsions as Vehicles for Transdermal Delivery of Aceclofenac AAPS Pharm Sci Tech 2007; 104:E1-E9.